DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
ATL-35

60 8th Street, N.E.
Atlanta, Georgia 30309

June 13, 2000

VIA FEDERAL EXPRESS

Roland Johnson
President
Blue Ridge Pharmaceuticals, Inc.
4249-105 Piedmont Parkway
Greensboro, North Carolina 27410

WARNING LETTER
(00-ATL-47)

Dear Mr. Johnson:

Investigator Robert L. Lewis conducted an inspection of [redacted] on May 23-25, 2000. Investigator Lewis conducted a preapproval inspection of your [redacted]. Our investigator documented several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause this product to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

You have failed to formally establish written procedures that would clearly define and describe the responsibilities and procedures applicable to the quality control functions associated with the manufacture of this product. Neither your firm, nor [redacted] had clearly assumed the responsibilities of a quality control unit for such critical functions as in-process review testing, review prior to product release, review of third party laboratory results, and initiation of investigation into out-of-specification (OOS) results. These quality control responsibilities should be clearly established prior to initiation of manufacturing at a contract site.

You instructed [redacted] to ship three lots of this product to a contract packager without any in process or release testing being performed. No evaluation was conducted of their conformance to established specifications prior to shipment to the packager or for a later clinical study. Release testing was finally conducted seven months after the lots were manufactured. This testing revealed one of the lots failed finished assay release specifications. There apparently were no procedures in place for the analytical lab or Blue Ridge to forward these results to [redacted] in a timely manner. There was no record available to substantiate the claim that these results had been forwarded to [redacted]

It is clear that your firm was aware of these OOS results no later than September 3, 1999. Your representatives (Michael Brinkley, Director of Pharmaceutical Services and Jody Lockhart, Director of Manufacturing and Quality Assurance) provided a record to Investigator Lewis of a conversation between Dr. Karla Henley of your staff and Dr. Dennis Bensley of FDA pertaining to these findings. The record stated that the analysis "brings up a process & quality control issue." It further states that your firm should "Be prepared to explain why it happened & have controls in place to prevent a recurrence" and to "submit explanation of high value, suggest any corrections & put in appropriate in-process controls". None of these actions were initiated.

You failed to conduct an investigation as required when a drug batch fails to meet its specifications. One of the three lots under stability study was found to fail assay testing at the "initial" test date (approximately seven months after manufacture). No investigation had been initiated when our inspection at [redacted] was completed. An investigation at this point would be difficult since none of the in-process samples were ever analyzed. This was reportedly due to delays in validating an analytical method and concerns over the integrity of the samples while at the test laboratory. Your firm also directed the destruction of the remaining portion of the three lots at [redacted]. Analysis of this product could have assisted in the investigation of the OOS result.

You could not provide documented evidence which established a high degree of assurance that the current manufacturing procedures and processes were effective and could consistently produce a product meeting its predetermined specifications and quality attributes. Your firm lacked sufficient data to justify the proposed manufacturing process for this product. One of the three initial lots failed release assay testing. There was also no data establishing the ability of the manufacturing process filed in your application to produce a homogeneous suspension. Although in-process samples were taken at various points during the manufacture of the three initial lots, none of the samples was ever analyzed. These initial lots were manufactured in the same manner and on the same scale as your proposed commercial process. You have failed to establish if the above lot failure was process related.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. At the close of the inspection, the Inspectional Observations (FDA 483) was issued to and discussed with [redacted] Mr. Brinkley of your firm was present for the discussion. A copy of the FDA 483 is enclosed for your review. The specific violations noted in this letter and in the FDA 483 could be symptomatic of underlying problems in your firm's quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deviations. Failure to promptly correct these deviations

may result in regulatory actions being initiated by the FDA without further notice. These actions include, but are not limited to seizure and/or injunction.

Please notify this office in writing within fifteen (15) days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your response should be sent to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,

Ballard H. Graham, Director
Atlanta District

Enclosure